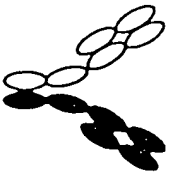


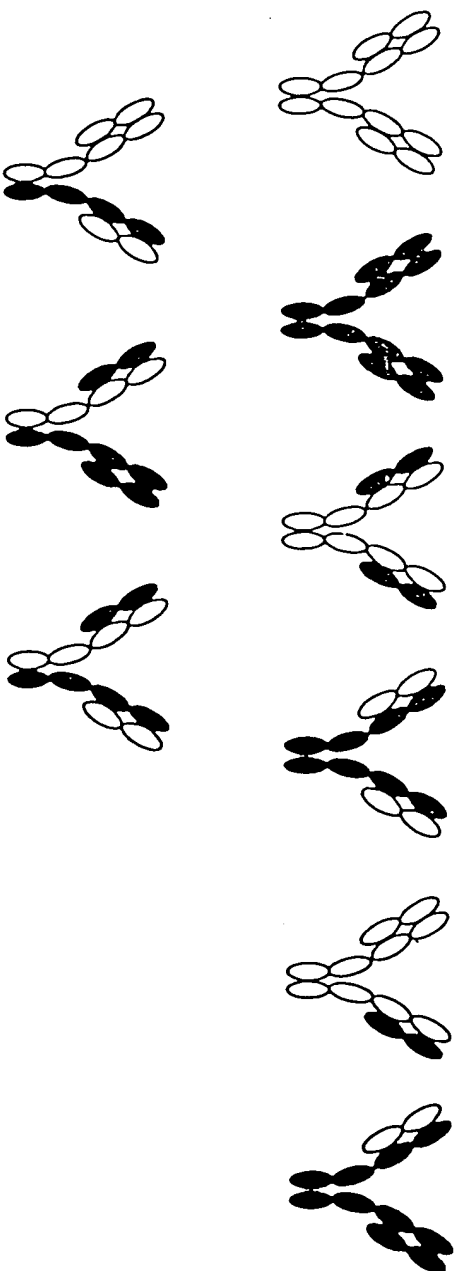
# A) Before engineering of CH3 domain

Fig. 1A

Target bispecific  
antibody



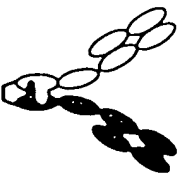
Possible contaminating species



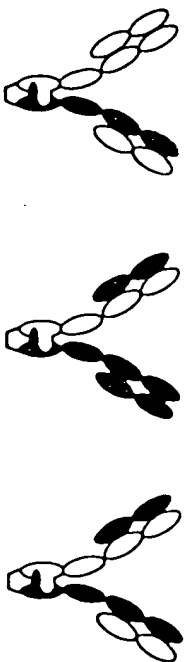
## B) After engineering of CH3 domain

Fig. 1B

Target bispecific  
antibody



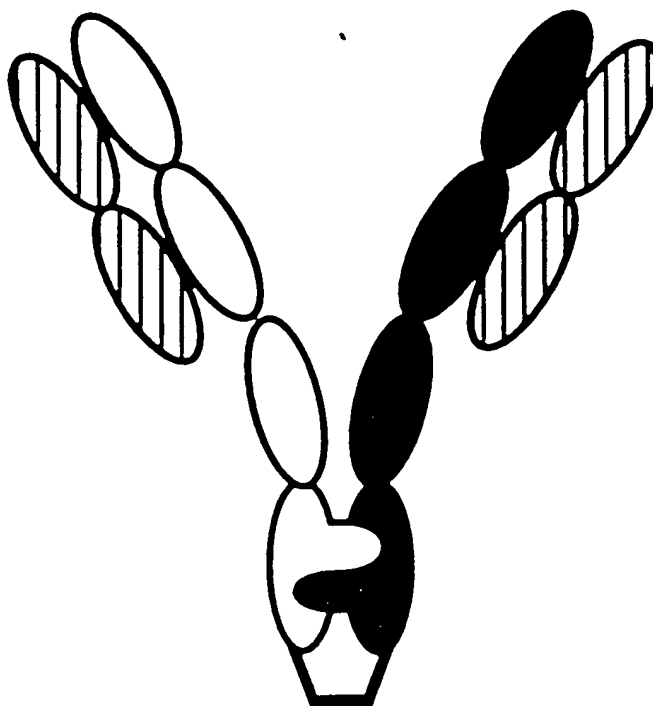
Possible major contaminating species



∨ = Engineered disulfide bond between CH3 domains

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Target bispecific  
antibody

Fig. 1C

Fig. 2A

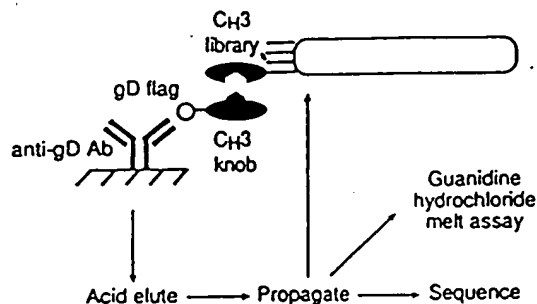


Fig. 2B

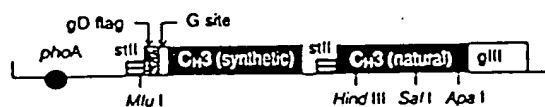


Fig. 2C

```

at11      → gD flag      → G site      → CH3
N A Y A L E H A D P H R F R C E D L A A N Y G O P
A A C G G C T A C G C T C T C A A A A T O C C G A C C G A A C C T T T T C T G C T A A G A T C T G C C A C A C T A C G C C A G C C
MluI      350      360      366      75

R E P O V Y T T L F P S R E E T T E M O V S L W C L
C G G A A C C T C A G G T G T A T A C C T T C C A C C C T C C A G A A A T C A C T A A A A C A C G T C T C T C T G T C C C T G
130

V E G F Y P S D I A V E M E S H C O P E N H Y T
C T C A A G C T T T C T A T C C G A G C G A T A T C C C T T G A A T G G A A G C A A C G G T C A A C C G C A A A C A C T A C A A A C C
225

T P F V L D S D C S F F L T S E L T V D E S R W O
A C T C C A C C G C T G C T G G A T T C T C A T G C C T C T T T T C T A T T C A A G C T C A C C T T C A A A A C C C G T T G C C A G
300

O G M V F S C S V H N E A L N H Y T O E S L S L
C A G G C A C G T T T C A G C T G T C T G T A T G C A C A G C C T T G C A C A C A C T A C A C C C A G A A A G C C T G C C C T G
375

S F C R O      N E E H I A F L L
T C T C C G C A A A T A A G C T C A G C C T C T C T A C A G G T C A G G T C A T T T T A T C A A A A A G A T A T C C C A T T T C T C T T G
→ at11      450

A S H F V F S I A T N A T A G O P R E P O V Y T T L
C A T C T A T T C T C T T T T T C T A T T C T A C A A A C C G T A C C T T G C C A G C C C C A G A A C C A C A G G T C T A C A C C T T G
→ CH3      525

P P S R E E N T E M O V S L T C L V E C F Y P S D
C C C A T C C C G G A A G A T G A C C A A A C C A G C T T G T A C T C C T T G C A A G C C T T C T A T C C C A G C C A C A
HindIII    600

I A V E M E S H C O P E N H Y T T T F F V L D S D
T C G C C C T G C A C T T G C A G A C A A T G C C A G C C C C A G A C A C T A C A A G A C A C C T C C G T C T G C A C T T G C A C
675

G S F P L T S F L T V D E S R W O O C H V F S C S
C C T C T C T T C T C T A C A G C T T T C T C A C C C T C A C A G A C A G C T G C A G C A G G C A C C T T C T C A T C T C C C
EcoRI      750

V H N E A L N H Y T O E S L S L S F C E A C P
T C A T G C A T C A G C T C T C A C A A C C A C T A C A C C A A A G C C T T C C T C T C C C G T A A T A G C C C C C
ApaI

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(SEQ ID NO: 13)

Fig. 3A

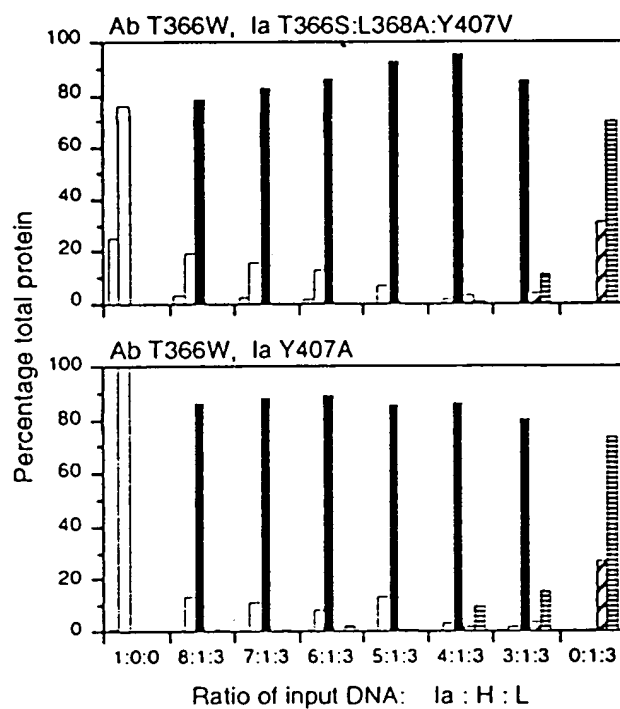


Fig. 3B

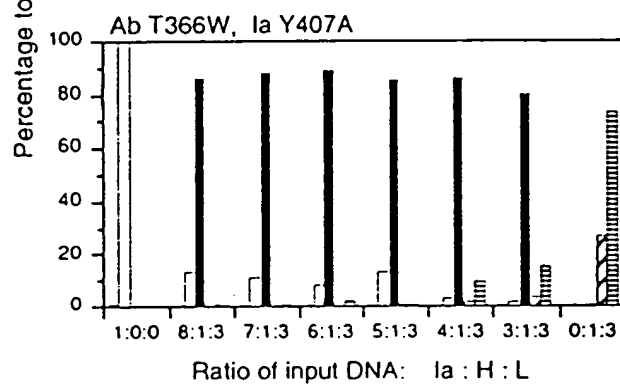
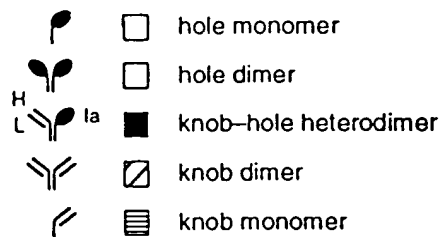


Fig. 3C



	1	20	abc	30	40	50
Ax1.78	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
Rse.23	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
Iger.MAT2C1G11	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
GCSFR.A4	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
Rse.04	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
obr.4	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
Rse.20	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
Rse.15	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
veg.f.5	QSVLTQ	PASVSGSPGQ	SITISCTGTSSD	VGGINVSWYQQHPG	KAPKLM	IEGSKRPSGV
		#####				###
		CDR L1				CDR L2

	60	70	80	90	a	100	
Ax1.78	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 14)
Rse.23	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 15)
Iger.MAT2C1G11	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 16)
GCSFR.A4	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 17)
Rse.04	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 18)
obr.4	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 19)
Rse.20	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 20)
Rse.15	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 21)
veg.f.5	SNRFSG	SKSGNTASLT	ISGLQAE	ADYYC	SSYTTRSTRV	FGG	TKLTVL (SEQ ID NO: 22)
		#####					###
		CDR L3					

Fig. 4

V<sub>H</sub>

her3.18 10 20 30 ab 40 50 a  
 QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYEMN--WVRQAPGKGLEWVSGISGSGGSTYY  
 \*\*\*\*\*  
 EVQLVESGPGGLVKPSQTLSTCTVSGGSISSGGYYWSWIRQHPGKGLEWIGYIY-YSGSTYY  
 obr.26 CDR H1 CDR H2

60 70 80 abc 90 100abcde 110 (SEQ ID NO: 23)  
 ADSVKGRFTISRDN SKNTLYLQMNRLRAEDTAVYYCARDNGWELTDWYFDLWGRGTMVTVSS

\*\*\*\*\*  
 NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVDLEDYGSGASDYWGQGTLVTVSS (SEQ ID NO: 24)  
 CDR H2 CDR H3

V<sub>L</sub>

her3.18 10 20 30 40 50 60  
 DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGAPSRF  
 obr.26 CDR L1 CDR L2

70 80 90 100 (SEQ ID NO: 25)  
 SGSGSGTDFTLTISLQPDFATYYCOOYSNYPLTFGGGTKLEIK  
 CDR L3

Fig. 5

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Percentage Identity of anti-ObR and anti-HER3 V<sub>L</sub>

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11
O1	49	47	51	81	60	48	76	51	<b>100</b>	62	51
O2	84	79	88	50	48	99	48	88	48	45	88
O3	83	82	85	51	50	95	49	85	49	46	85
O4	47	50	51	83	77	48	65	51	73	64	51
O5	49	47	51	81	60	48	76	51	<b>100</b>	62	51
O6	83	79	86	50	50	99	47	86	48	45	86
O7	81	<b>100</b>	86	51	49	80	48	86	47	44	86
O8	81	<b>100</b>	86	51	49	80	48	86	47	44	86
O9	81	<b>100</b>	86	51	49	80	48	86	47	44	86
O10	83	79	85	50	49	98	46	85	48	45	85
O11	83	80	87	50	49	99	47	87	48	45	87
O12	81	<b>100</b>	86	51	49	80	48	86	47	44	86
O13	49	47	51	81	60	48	76	51	<b>100</b>	62	51
O14	50	50	54	95	67	49	76	54	75	62	54
O15	82	79	85	49	48	97	46	85	47	44	85
O16	84	80	87	50	49	<b>100</b>	47	87	48	45	87
O17	45	44	47	65	62	45	62	47	62	<b>100</b>	47
O18	50	51	50	75	79	50	63	50	66	62	50

O1-O18: Anti-Ob-R antibody clones obr. 1, 11, 12, 14, 15, 16, 17, 18, 19, 2, 20, 21, 22, 23, 24, 26, 3, 4, respectively.

H1-H11: Anti-HER3 antibody clones her3.1, 3.10, 3.11, 3.12, 3.16, 3.18, 3.19, 3.22, 3.3, 3.4, 3.7, respectively.

Fig. 6